

## RESEARCH ARTICLE

# Solitary Fibrous Tumor: A Retrospective Study on Histopathologic Features and Immunohistochemistry Staining at Cipto Mangunkusumo Hospital

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## Abstract

*Solitary fibrous tumor (SFT), is a rare mesenchymal spindle cell tumor and its biological behavior is hard to predict. There is no characteristic clinical manifestation and morphologic features showed broad spectrum, so often diagnosed as other spindle cell mesenchymal tumor, benign or malignant. In most cases, immunohistochemistry staining (IHC) is needed to diagnose SFT. The aim of this retrospective study is to see demographic data, histopathological features and the importance of IHC staining diagnosis of SFT. Secondary data was obtained from Department of Anatomical Pathology, Faculty of Medicine, Universitas Indonesia in 2010-2016. There were 35 samples included in this review; most are male (20 cases) aged <55 years old. Thirty one cases were in the extrapleural site and most of the tumor is less than 5 cm in diameter. There are 20 cases of cellular SFT while the other is fibrous SFT. Commonly, cellular SFT shows moderate cellularity and pleiomorphism. Fibrous SFT are well circumscribed and without necrosis. There are only 3 cases of malignant SFT which is located in intra-abdominal and orbit. Generally, SFT is benign, small, and well circumscribed. Most of the cases are cellular than fibrous; mild to moderate nuclear pleiomorphism, mitotic activity low, and without necrotic. Features of malignant SFT are hypercellularity, moderate to high nuclear pleiomorphism, mitotic >4/10 high power field (HPF) and necrosis. Most SFT are benign, some may recurrence and metastasize.*

**Keywords:** solitary fibrous tumor; cellular; fibrous; malignant; immunohistochemistry.

## Solitary Fibrous Tumor: Studi Retrospektif Gambaran Histopatologis dan Pulasan Imunohistokimia di Rumah Sakit Cipto Mangunkusumo

## Abstrak

*Solitary fibrous tumor (SFT), tergolong tumor mesenkimal jenis sel spindel yang jarang ditemukan dan sifat biologiknya sulit diprediksi. Gambaran klinik SFT tidak khas dan gambaran morfologiknya berspektrum luas sehingga sulit dibedakan dengan tumor mesenkimal sel spindel yang lain baik jinak maupun ganas. Pada sebagian besar kasus, diperlukan pemeriksaan imunohistokimia (IHK) untuk menegaskan diagnosis SFT dan menyingkirkan diagnosis banding. Studi retrospektif ini bertujuan mengetahui karakteristik demografik, gambaran histopatologik dan pentingnya pulasan IHK dalam mendiagnosis SFT. Data sekunder berasal dari catatan medik Departemen Patologi Anatomi FKUI/RSCM tahun 2010-2016. Gambaran histopatologik yang dinilai meliputi simpai, pola histopatologik, selularitas, pleomorfisme, mitosis, nekrosis, rekurensi serta metastasis. Dari 35 sampel yang dapat dianalisis terdapat lebih banyak subjek laki-laki yaitu 20 kasus dan usia <55 tahun yaitu 29 kasus. Lokasi ekstrapleura lebih banyak ditemukan yaitu 31 kasus dibandingkan pleura (4 kasus). Tumor berukuran kecil (<5 cm) lebih banyak yaitu 21 kasus. Sebagian besar SFT berbatas tegas dan SFT selular lebih banyak dari fibrous, yaitu 33:13. SFT selular umumnya menunjukkan selularitas tinggi dengan pleomorfisme sedang, sedangkan SFT fibrous dengan selularitas dan pleomorfisme sedang. Mitosis 0/10 LPB dan tanpa nekrosis. Didapatkan 3 kasus yang memenuhi kriteria SFT ganas dengan hiperselularitas inti pleomorfik, nekrosis dan mitosis >4/10LPB. Rekurensi ditemukan pada 5 SFT jinak.*

**Kata kunci:** solitary fibrous tumor; selular; fibrous; maligna; imunohistokimia

## Introduction

Solitary fibrous tumor (SFT) is fibroblastic mesenchymal tumor; occur in <2% of all soft tissue tumor and <5% of all pleural primary tumor.<sup>1,2</sup> Patients aged were range from 20-70 years old and reach highest incident in 5<sup>th</sup> decade. No gender predilection was found. Extrapleural SFT can be found in subcutaneous tissue, inner extremities soft tissue, retroperitoneum, abdominal cavity, head and neck including orbital, meninges and visceral organs such as thyroid, liver, gastrointestinal track, prostate and salivary glands.<sup>3-5</sup>

SFT is a grayish, solitary, multinodular, well circumscribe mass with 5-10 cm in diameter and located subcutaneous. Histologically, it shows patternless architecture with combination of cells and fibrous stroma. It shows both hypercellular and hypocellular area with collagenous and hyalinised stroma. In some cases, staghorn and hyalinised vessels can be prominent. The nucleus is oval to spindle, with a little cytoplasm with indistinct borders. Malignant SFT is characterized with high cellularity, increase mitotic activity (more than 4/10 HPF), nuclear pleiomorphism, necrosis, and infiltrative border.<sup>6-8</sup>

SFT is a slow growing tumor, with clinical manifestations may arise from pressure effect to nearby organs. Hypoglycemia is present in 5% cases of SFT due to the production of insulin-like growth factor (IGF).<sup>5-9</sup> Imaging studies such as CT-scan and MRI show non-specific well circumscribed masses with heterogeneous intensity.<sup>10</sup>

It is difficult to diagnose SFT histopathologically only, because their morphology is unspecific, pattern less, from fibrous to cellular. Differential diagnoses for SFT are mesenchymal tumors with staghorn vessel and perivascular hyalinization, cellular schwannoma, benign fibrous histiocytoma, spindle cell lipoma, hemangioma, monophasic synovial sarcoma, malignant peripheral nerve sheath tumor (MPNST) and dedifferentiated liposarcoma.

SFT can be confirmed by immunohistochemistry (IHC) staining using CD34, CD99 and Bcl-2, although less specific. About 5-10% cases show negative CD34 staining.<sup>11</sup> The most sensitive and specific IHC staining for SFT is STAT6, known by genes fusion NAB2 and STAT6.<sup>12-14</sup>

Most of SFT are benign but the behavior of this tumor is unpredictable. Recurrence and metastasis occur in 5-10% cases of benign SFT and 20-30%

cases of malignant SFT.<sup>3</sup> Although there is no association between histopathology features to the behavior of the tumor, high mitotic activity in malignant SFT is an indicator of poor prognosis.<sup>1</sup> Complete excision and long term follow up is required in both benign and malignant SFT.

The purpose of this review is to describe the demographic and histopathological features of SFT that resemble other spindle cell tumor (benign or malignant) and the importance of immunostaining to exclude differential diagnosis.

## Methods

This is a retrospective, descriptive, cross sectional study. Secondary data were obtained from the medical record of the Department of Anatomical Pathology, Faculty of Medicine, Universitas Indonesia, Dr. Cipto Mangunkusumo Hospital from January 2010 to December 2016. The morphological code used according to International Classification of Disease-10 (ICD-10) was M8815/1 and M8815/3 for malignant SFT and M.9150/0, M.9150/1 and M.9150/3 for hemangiopericytoma for archive before 2013. Tumors were taken from any site of body through biopsy or surgical procedure. All requisitions forms, histopathology slides and IHC slides were collected and reviewed by the researchers (NCS and AA).

The inclusion criteria for the study are all cases diagnosed as SFT or hemangiopericytoma by H&E staining and/or IHC. Incomplete or unrepresentative slides and SFT/HPC located in central nervous system are excluded from the study.

The researchers review H&E slides for tumor borders, pattern, cellularity, nucleus pleiomorphism, necrosis, mitotic activity as in Demicco,<sup>16</sup> and IHC. We also evaluate the recurrence and metastasis.

## Results

There were 53 cases of SFT and hemangiopericytoma retrieved in this study. Eighteen cases (ten with incomplete data and eight cases were located at CNS) were excluded from the review. Demographic characteristic, size and location of the tumor were recorded. From 35 cases, 27 of them have been confirmed by IHC staining. Most of the patients were male and above 50 years old. Demographic and characteristic of SFT is shown in Table 1.

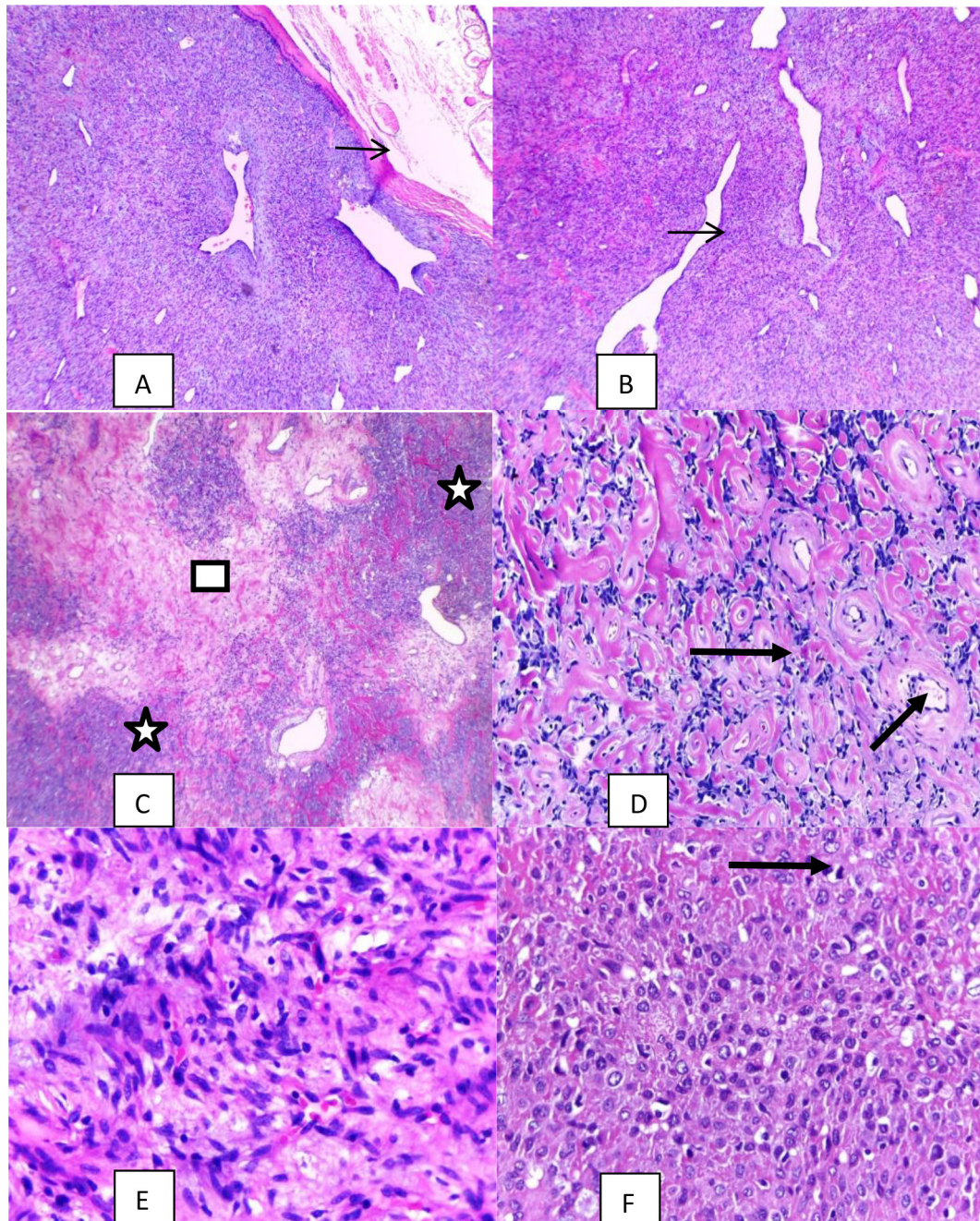
**Table 1. Patients Demographic and Characteristic of SFT**

| Characteristic   | n  |
|------------------|----|
| Age              |    |
| <55 year old     | 29 |
| ≥55 year old     | 6  |
| Sex              |    |
| Male             | 20 |
| Female           | 15 |
| Location         |    |
| Pleural          | 4  |
| Extra pleural    | 31 |
| Head-neck        | 23 |
| Extremities      | 2  |
| Intra-abdomen    | 5  |
| Trunks           | 1  |
| Size in diameter |    |
| <5 cm            | 21 |
| 5-10 cm          | 8  |
| >10 cm           | 6  |
| Procedure        |    |
| Operation        | 26 |
| Biopsy           | 9  |

Microscopically, SFT is pattern less, tumor dominated with cellular or fibrous component. (Fig. 1) Most of the tumors features between cellular and fibrous component, with moderate cellularity and pleiomorphism, with no mitotic activity. There

were only 3 cases diagnosed as malignant SFT (Fig. 1F). Criteria of malignancy in the SFT based on WHO classification of soft tissue and bone tumor is characterized by increased cellularity, mitoses >4/10 HPF, nuclear pleiomorphism, necrosis and or infiltrative border.





**Figure 1. Histopathology of SFT.** A. Well circumscribed tumor → (40x). B. Cellular SFT: uniform tumor cell, staghorn vessels → (40x). C. Fibrous SFT: patternless, hypocellular (□) and hypercellular (☆) (40x). D. Perivascular hyalinization → (40x). E. Oval to spindle shape nuclei (400x). F. Malignant SFT with nuclear pleomorphism with mitotic activity → (400x)

Both cellular and fibrous SFT have well circumscribed border, moderate cellularity and mild to moderate nuclear pleomorphism. Necrosis was found in all malignant cellular SFTs and one case of benign fibrous SFT (Table 2). From 3 malignant

SFTs, two are located intra- abdomen and the other is located in orbit. All of malignant cases size were >5 cm and mitoses >3/10 HPF, with moderate to high cellularity and prominent nuclear pleomorphism.



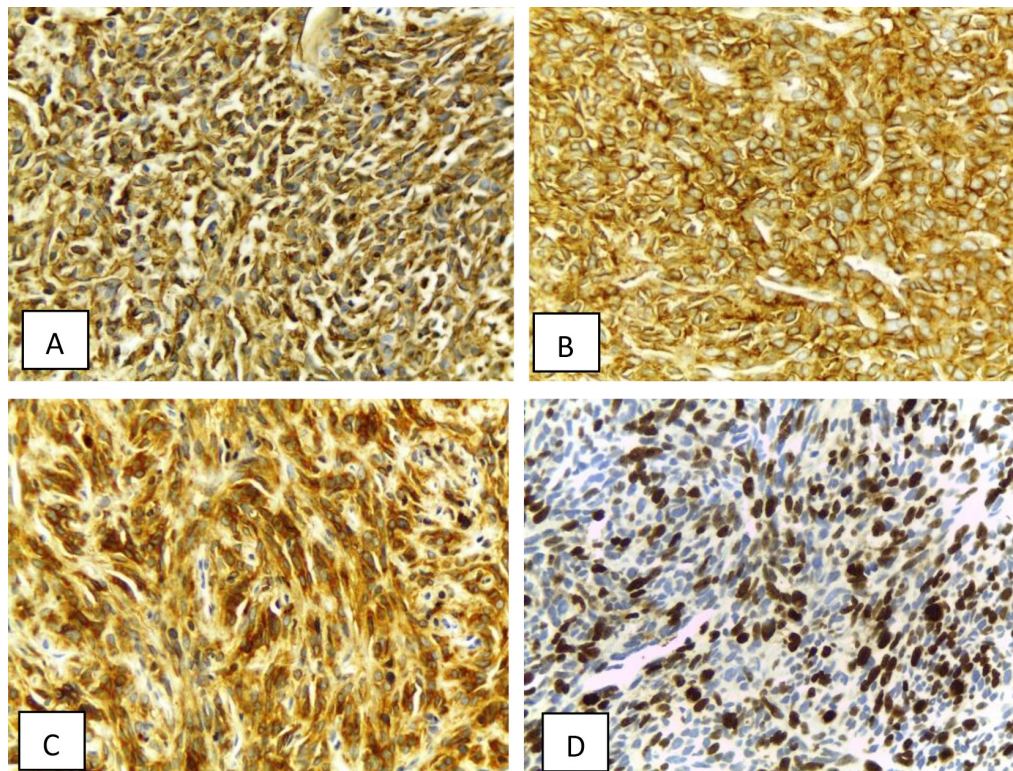
**Table 2. Comparison between Cellular and Fibrous SFT**

| Histopathologic features          | Cellular SFT (n=22) | Fibrous SFT (n=13) |
|-----------------------------------|---------------------|--------------------|
| Border                            |                     |                    |
| Well circumscribed                | 13                  | 11                 |
| Poorly circumscribed/infiltrative | 9                   | 2                  |
| Cellularity                       |                     |                    |
| Mild                              | 4                   | 3                  |
| Moderate                          | 13                  | 8                  |
| High                              | 5                   | 2                  |
| Pleomorphism                      |                     |                    |
| Mild                              | 7                   | 4                  |
| Moderate                          | 12                  | 9                  |
| Severe                            | 3                   | 0                  |
| Mitosis                           |                     |                    |
| 0/10 HPF                          | 19                  | 11                 |
| 1-3/10 HPF                        | 0                   | 2                  |
| ≥ 4/10 HPF                        | 3                   | 0                  |
| Necrosis                          |                     |                    |
| Negative/minimal (<10 %)          | 19                  | 12                 |
| Positive (≥10 %)                  | 3                   | 1                  |
| Recurrence                        | 3                   | 2                  |
| Mitosis                           | 0                   | 0                  |

Twenty seven of 35 cases were stained with IHC to confirm the diagnosis. CD34 is the most common IHC used. Only 13 cases (9 cellular SFT and 4 fibrous SFT) were completely stained with combination of CD34, CD99 and Bcl-2. (Table 3). CD34, CD99 and Bcl-2 were considered positive if more than 10% areas of the tumor cells were strongly stained (Fig. 2). All of the antibodies showed diffuse staining in SFT. IHC is also used to exclude differential diagnosis.

**Table 3. IHC Staining of Cellular SFT and Fibrous**

| IHC Staining | Cellular (n=9) | Fibrous (n=4) |
|--------------|----------------|---------------|
|              | Positive       | Positive      |
| CD34         | 9/9            | 3/4           |
| CD99         | 8/9            | 3/4           |
| Bcl-2        | 8/9            | 3/4           |
| Ki-67>15%    | 2/9            | 0/4           |



**Figure 2. Immunoprofile of SFT.** A. CD34, positive diffuse in cytoplasm. B. CD99 positive diffuse in membrane. C. Bcl-2 positive diffuse in membrane and cytoplasm. D. Ki67 in malignant SFT, positive diffuse in 79% nuclei (IHC, 400x).

## Discussions

Previously, SFT can be found in serous tissue such as in pleural, pericardial and peritoneal. However, later, SFT can be found anywhere.<sup>15-17</sup> Ratio between pleural and extra- pleural SFT has not been documented well due to limited cases. Both have similar clinical manifestation and microscopic appearance.<sup>3,7</sup> Gold et al<sup>1</sup> reported 30-40% cases of SFT were extrapleural. Outside thorax cavity, SFT is commonly found in soft tissue extremities and orbit.

In this review, we found 31 cases of extrapleural SFT (89%) and only 4 cases (11%) pleural SFT. From 31 cases of extrapleural SFT, majority of the cases (23 cases) are located in head and neck, 5 cases in intra-abdomen/pelvis, 2 cases in the extremities and one case in the trunk. Tumor location is not in line with the result of Demicco et al<sup>16</sup> who studied 110 cases of SFT and found less pleural than extrapleural SFT (31:79 cases). However, most of their extrapleural SFT are located in the abdomen (37 cases), followed by 18 cases in the extremities and 12 cases in head-neck and trunks.

Of the 23 cases of head-neck SFT, there are 16 cases located in the orbit. Westra et al<sup>18</sup> first reported orbital SFT in 1994. Kao et al<sup>19</sup> reported 36 cases of head-neck SFT composed of 12 cases of oral cavity, 11 from orbital, 6 from nasal and 7 cases of head-neck soft tissue. Orbital SFT may originate from the lacrimal sac, lacrimal fossa, conjunctiva and sclera. In 2010-2016, there is an increase number of SFT diagnosed with the highest number in 2016.<sup>15,20</sup>

Molecular studies of SFT have been started in 2014. Fritchie et al<sup>21</sup> proved there were NAB2-STAT6 gene fusion in >95% of SFT including meningeal hemangiopericytoma. Doyle et al<sup>14</sup> reported expression of STAT6 in the nuclei in 98% cases of SFT can be used as a surrogate marker of NAB2-STAT6 gene fusion. Various studies showed the same result.<sup>11-13,22</sup>

From 35 cases of SFT, 20 cases are male and 15 cases are female. Median age of the patients is 39 years old (range 14-68 years old). According to the literature, the ratio of male and female is 3:2 ranged in 20-70 years old.<sup>3</sup> The tumor rarely occurred in children and elderly. The youngest patient with SFT is 2 years old.<sup>23</sup> In our study, the youngest patient is 14 years old.

A total of 21 cases (60%) in our study were <5 cm in diameters. Eight cases were measured between 5-10cm, and 6 cases with size more than 10cm and located in intra- abdomen and extremities. Gold et al<sup>1</sup> reported tumor size > 10cm is correlated with poorer prognosis. Unfortunately we did not have follow up

data of the patient, except for 5 cases that recidive in 1-2 year time. A multicenter study conducted by Von Houdt et al<sup>24</sup> reported that tumor size more than 10 cm and increase mitotic activity are correlated to a significant increase of metastatic. Bishop et al<sup>25</sup> studied 13 cases of malignant reported that the average size of tumor is 13,4 cm and can be located in at any site of the body.

Malignancy criteria of SFT were originally described by Vallat-Decouvelaere et al<sup>26</sup> based on nuclear pleiomorphism, hypercellularity, mitoses  $\geq 4/10$  HPF, and necrosis. WHO classification of soft tissue and bone tumor criteria for malignant SFT are: hypercellularity, mitoses  $\geq 4/10$  high power fields, pleiomorphic nuclei, necrosis and or infiltrative border.<sup>15</sup> Marino-Enriquez et al<sup>9</sup> stated that higher mitosis is the most reliable criteria of malignant SFT.

In this study, we found that fibrous SFT shows moderate cellularity and moderate pleomorphism, while cellular SFT shows high cellularity and moderate pleomorphism. Demicco et al<sup>12</sup> concluded fibrous SFT showed high cellularity, moderate pleomorphism and cellular SFT are dominated by high cellularity and mild pleomorphism.

There are 3 variants of SFT: 1) classic pattern less with spindled to ovoid fibroblastic cells, prominent vascular pattern, varying component of fibrous stroma and occasional multinucleated stromal giant cells (giant cell angiofibroma) (Fig 3A and 3B) and lipomatous (fat-forming) SFT, 2) malignant SFT, and 3) dedifferentiated SFT.<sup>7,9</sup>

We found 3 interesting cases in this review. First is a giant cell-rich SFT (formerly known as giant cell angiofibroma). Clinical presentation as a mass in right ear canal. At first it was diagnosed as a HPC. After reevaluation, it was diagnosed as a mesenchymal tumor that difficult to determine the origin and type of the malignancy and final diagnosis without IHC is a soft tissue tumor suspect malignancy with differential diagnosis of malignant peripheral nerve sheath tumor (MPNST) and inflammatory myofibroblastic tumor. IHC staining shows diffuse CD34 and CD99 positive tumor cell and only 1-2% positivity in Ki-67 staining. Based on this finding the case is diagnosed as SFT.<sup>9</sup>

Second case is consultation from other hospital, a retroperitoneal mass that initially was diagnosed as a hemangiopericytoma in 2014. After reviewing the H&E slide, we favored as malignant myopericytoma and angiosarcoma as differential diagnosis. Immunostaining was performed and the result showed strong, diffuse vimentin and CD34 positivity, also positive for neuron specific enolase

(NSE), moderately positive with smooth muscle actin (SMA), negative with CD31, muscle-specific actin (MSA) and desmin, S100 non-specific, and Ki67 < 10%. IHC result concluded the case as SFT.

Third case is a lobulated sinonasal mass, initially diagnosed as a malignant tumor (MPNST) possibly due its clinical appearance. EMA, CD99 and Bcl-2 staining are positive and Ki-67 positive for 10% of cells, while CD34, CD31 and SMA staining were negative. Even the IHC staining is not typical, morphologic and IHC staining concluded this case as a SFT. Unfortunately confirmation using STAT6 was not done because it is not available in our institute.

IHC examination in this review showed all cases of cellular SFT are positive stained with CD34, 89% stained with CD99 and 89% stained with Bcl-2. While fibrous SFT were only 75% stained with CD34; CD99, and Bcl-2. We found diffuse positivity in both cellular and fibrous SFT. Goldblum et al<sup>7</sup> reported that cellular SFT only positive for CD34 in fewer cases, stained weak and less diffuse rather than fibrous SFT. In contrast, previous studies showed that SFT express CD34 in 90% cases, CD99 in 70% cases and Bcl-2 in only 30% cases. CD34 negative were found in 5-10% cases of SFT and cannot exclude the SFT diagnosis.<sup>9</sup> Schulz et al<sup>27</sup> reported weak expression of CD34 in malignant SFT. Negative CD34 staining were found in recurrent tumor and malignant transformed tumor.<sup>28,29</sup> STAT6 staining has >95% sensitivity and 100% specificity for diagnose SFT.<sup>11,13,14</sup>

Differential diagnosis for SFT, such as cellular schwannoma showed strong diffuse positive staining with S-100. Monophasic synovial sarcoma is usually positive with CD99 and Bcl-2 but negative for CD34 (95% cases) and strong positive with TLE1. MPNST is focally positive with S-100 and 50% cases positive glial fibrillary acidic protein (GFAP). Other tumor which are usually positive for CD34 is (1) Spindle cell lipoma consist of fat cell and positive diffuse with CD34, although the staghorn vessel is less in spindle cell lipoma. (2) Deep fibrous histiocytoma is generally firmly and positive CD34 staining but it shows storyform pattern, while SFT is pattern less. (3) Hemangioma is positive for CD31 and glucose transporter-1 (GLUT-1).<sup>9</sup>

We found recurrence in 3 cases of benign SFT located in orbit (2 cases) and sinonasal (1 case). Baldi et al<sup>29</sup> studied 14 cases of late recurrence SFT (recurrent occur after 10 years of first diagnosis), they found five of the cases were formerly benign and other seven cases were formerly malignant. They also found 4 from 5 metastatic cases were benign SFT. They concluded that recurrence may

occur form benign SFT. Local recurrence incidence in 10 and 20 years are 19,2% and 38,6% while metastatic recurrence incidence in 10 and 20 years are 31,4% and 49,8%. Long term monitoring is necessary for SFT.<sup>30</sup>

## Conclusions

SFT were found more in male than female. Extrapleural SFT is more common than pleural SFT. Majority of SFT is benign, with <5 cm in diameter and well circumscribed, with cellular pattern is most common. Cellular type is more common than fibrous type. Recurrence is more common in orbit area and malignant SFT is in intra-abdominal (pleural SFT) and orbit. IHC staining is required for the diagnosis SFT and exclusion of differential diagnosis.

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